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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/751,346	01/02/2004	Ron S. Israeli	41426-FA-PCT-US/JPW/CY	7618

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EXAMINER	
YAO, LEI	
ART UNIT	PAPER NUMBER
1642	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/751,346	ISRAELI ET AL.	
	Examiner	Art Unit	
	Lei Yao, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,23-25,27 and 29-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21, 23-25, 27, and 29-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Request for Continued Examination

The request filed on 11/5/2007 for a Continued Examination (RCE) under 37 CFR 1.114 based on Application No. 10751346 is acceptable, and a RCE has been established. An action on the RCE follows.

Claims 21, 23-25, 27, and 29-31 are pending and are examined on the merits for a method of eliminating prostate cancer comprising providing the antibody coupled to cytotoxic agents.

Priority

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

It is noted that this application is continuation of 08/894583, filed 2/23/1998, which is 371 national stage of US application, of PCT/US96/02424. Upon review of specification of the application of 08/894583 and PCT/US96/02424, the applications as filed although state, on paragraph 165, "therapeutic agent comprising antibodies or ligand(s) directed against PSM antigen and a cytotoxic agent conjugated thereto or antibodies linked enzymes which activate prodrug to kill the tumor, the cytotoxic agent may either be a radioisotope or toxin", they do not provide adequate **support** for claimed method of eliminating cancerous prostate epithelial cells comprising providing an antibody bound to a cytotoxic agent which antibody binds to an outer membrane domain of prostate specific membranes antigen (PSMA) having the sequence of SEQ ID NO: 128. There are no antibodies to the outer membrane of PSMA and/or the antibodies bound (here interpreted as having affinity to) to a cytotoxic agent are described, contemplated or used for the claimed method. Therefore, The Office is giving currently filing date, 1/2/2004, for the instant claims 21, 23-25, and 27-31.

In the remarks filed on 11/5/2007, applicant states that the specification of originally filed application PCTUS96/02424 has the support for the newly amended claim reciting that the

antibody binds to an outer membrane domain, by stating "with the protein sequence information, antigenic areas may be identified and antibodies directed against these areas may be generated and targeted to the prostate cancer for imaging the cancer or therapies" or "antigen has the characteristics of a membrane spanning protein with the majority of the protein on the exofacial surface". These statements do not support the clamed method of contacting or administering the antibody that binds to an outer membrane of the PMSA in the cells because binding to the an outer membrane of the PMSA expressed on the surface of the prostate cancer cell does require a specific antibody that has been mapped or tested to specifically bind to the outer membrane of the protein. In addition, the antibodies contemplated in the specification including 7E11 and CYT-356 are the antibodies binding to the intracellular domain of the PMAS. Therefore, the priority established for the pending claims are 1/2/2004 as stated above.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter Rejection

Claims 21, 23-25, 27, and 29-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

It is noted that the claims as newly amended recite "an antibody bound to a cytotoxic agent..", which is not supported by instant specification. Instant specification as filed, although contemplate a method of eliminating the prostate cancer by antibody linked (coupled) to a cytotoxic agent, do not reciting the antibody bound to a cytotoxic agent. The currently amended

claims would also be understood or interpreted by the skilled in the art as the antibody having the affinity to (bound to) the cytotoxic agent, which is NOT supported in the instant specification. Amending the term "antibody bound to…" in the claims to "antibody linked to…", antibody coupled to…", or antibody conjugated to… etc being supported by the instant specification would obviate the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 21, 23, 25, 27, and 29-31 are rejected under 35 U.S.C. 102 (b) as being anticipated by Murphy et al., (WO9947554, Publication Date 9/23/1999) as evidenced by sequence search result.

The priority given for the pending claims is 1/2/2004 as stated above.

The claims are drawn to a method of eliminating cancerous prostate epithelial cells cancerous prostate epithelial cells comprising: providing an antibody bound to a cytotoxic agent which antibody binds to an outer membrane domain of prostate specific membrane antigen (PMSA) having the sequence set forth in SEQ ID N0:128 and contacting said cells with the antibody bound to the cytotoxic agent under conditions effective to permit both binding of the antibody to the outer membrane domain of the prostate specific membrane antigen and eliminating said cells, wherein the cytotoxic agent is a toxin, radioactive or chemotherapeutic agent, wherein the contacting is administering and wherein the antibody is in a composition comprising diluent or physiologically acceptable carrier.

Since no definition is provided in the specification for the term "an antibody bound to a cytotoxic agent" recited in the claims as stated in the new matter rejection above, the term is interpreted as an antibody conjugate comprising an antibody linked to a cytotoxic agent. In addition, for the rejection here the outer membrane domain of the prostate specific membrane antigen (PSMA) is interpreted as an extracellular domain of PSMA on the surface of a prostate cell.

Murphy et al., disclose a method of treating prostate cancer with an antibody to prostate specific membrane antigen (PSMA) conjugated with a cytotoxic agent (section 5.4.3, page 26-29). Murphy et al., first disclose (provide) the antibodies to the extracellular domain (outer membrane domain) of the PSMA protein and the PSMA having the amino acid sequence identical to the claimed sequence of SEQ ID NO: 128 as evidenced by the search result (attached, table 2). Murphy et al., then disclose that the antibodies conjugated with radioactive, cytotoxic or chemotherapeutic molecules in a pharmaceutical composition is in vivo administered (contacting) to a prostate cancer patient to kill the malignant cells or tissues expressing the PSMA protein for the prostate cancer therapy (page 5 and 27). Murphy et al., specifically disclose that the antibodies recognize the extracellular membrane domain of the PSMA protein expressed in the prostate cancer cell LNCap by FASC analysis (figure 7 and 12, page 7 and 9).

For this rejection the preamble of eliminating cancerous prostate epithelial cells does not limit the claims because the only active steps in these claims are providing antibody conjugate, and contacting the cells, and/or administering the patient with the antibody conjugate. The methods of Murphy et al., disclose the same method steps, the same materials and treating the same patient population, which would inherently have the same treatment result of eliminating the cancerous prostate epithelial cells. Therefore, the reference discloses each and every limitation of the claimed method.

2. Claims 21, 23-25, 27, and 29-31 are rejected under 35 U.S.C. 102(b) as being anticipated by Horoszewicz et al., (US Patent, 5162504, Nov, 1992, provided in the Office action dated 11/9/2005) as evidenced by Horoszewicz et al., (Anticancer Res, vol 7, page 927-35, 1987, provided in the Office action dated 11/9/2005) and Murphy et al., (WO9947554, Publication Date 9/23/1999)

Claims 21, 23, 25, 27, and 29-31 are set forth above, wherein the administering is carried out intravenously (claim 24).

Since no definition is provided in the specification for the term "an antibody bound to a cytotoxic agent" recited in the claims as stated in the new matter rejection above, the term is interpreted as an antibody conjugate comprising an antibody linked to a cytotoxic agent. In addition, for the rejection here the outer membrane domain of the prostate specific membrane antigen (PSMA) is interpreted as an extracellular domain of PSMA on the surface of a prostate cell.

Horoszewicz et al., disclose a method of treating prostate cancer with an antibody conjugate comprising prostate specific membrane antigen (PSMA, col 7, col 11-13). Horoszewicz et al., first disclose (provide) that the antibodies to PSMA is conjugated to a radioactive, cytotoxic or chemotherapeutic molecule for treating human prostate carcinoma patient with a pharmaceutical carrier or diluent (col 7, 11-12). Horoszewicz et al., further disclose that conjugated antibodies can be administered, such as intravenously, to the patients to enhance antitumor effects through the cytotoxic action (col 11-13, col 13, line 7-13). Horoszewicz et al., disclose antibody to the PSMA, 9H10-A4, only recognizes the surface of prostate cancer cells, LNCap (fig 3 and col 7, line 66+) as evidenced by Horoszewicz et al., (Anticancer Res, abstract, line 10-12).

The antibodies comprising 9H10-A4 recognizing only the surface of PSMA of prostate cancer LNCap cell, in the reference appears to meet the requirements of the instant claims regarding to the antibody binding to outer membrane domain of PSMA of SEQ ID NO: 128 because LNCap cell express PSMA protein of SEQ ID NO:128 as evidenced by Murphy et al. The Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

For this rejection the preamble of eliminating cancerous prostate epithelial cells does not limit the claims because the only active steps in these claims are providing antibody conjugate and contacting the cells, and administering the patient with the antibody conjugate. The methods of Horoszewicz et al., disclose the same method steps, the same materials and treating the same patient population , which would inherently have the same treatment result of eliminating the cancerous prostate epithelial cells.

Rejection under 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 21, 23-25, 27, and 29-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horoszewicz et al (US Patent, 5162504, Nov, 1992) in view of Liu et al (Cancer Research. Vol 57, page 3629-34, 1997) as evidenced by sequence search result and Israeli et al (Cancer Res. vol 53, page 227-230, 1993).

Since no definition is provided in the specification for term "an antibody bound to a cytotoxic agent" recited in the claims, the term is interpreted as an antibody conjugate comprising an antibody linked to a cytotoxic agent. In addition, for the rejection here the outer membrane

domain of the prostate specific membrane antigen (PSMA) is interpreted as an extracellular domain of PSMA on the surface of a prostate cell.

The teaching of Horoszewicz et al., are set forth above. Because Horoszewicz et al., do not specifically disclose the sequence of PMSA, the reference does not clearly teach whether the PSMA protein has the sequence of SEQ ID NO: 128 and the antibody specifically binding to the protein of SEQ ID NO: 128.

Liu et al., first teach that the antibodies binding to the intracellular domain of PSMA is not available for the viable cells binding. Liu et al., then teach the antibodies, J591, J533, and J415 that react with the extracellular domain (outer membrane) of PSMA expressed in the prostate cancer and prostate cancer epithelial cells and teach the antibodies are weak or non staining in the normal prostate tissues and vascular endothelium (figure 3, bridging page 3631-2 and abstract,). The PSMA of Liu has the identical amino acid sequence of SEQ ID NO: 128 as evidenced by sequence search result and Israeli et al. Liu et al also teach that antibodies demonstrate a significant improvement in vivo targeting for imaging and therapy (page 3633, col 2, last paragraph) and suggest that those antibodies should prove useful for in vivo targeting to prostate cancer (abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the methods of Horoszewicz et al., and Liu et al., to eliminate the prostate cells by administering the antibody conjugate with predictable result. One of ordinary skill in the art at the time the invention was made would have been motivated to substitute the antibody in the method of Horoszewicz et al., with any one of the antibodies of Liu et al in order to benefit for the prostate cancer treatment by specifically targeting the PMSA expressing prostate cancer cells because Liu et al suggest that those antibodies can access to the cell surface and significantly improved in vivo targeting for therapy. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for combining the teachings in the method because Horoszewicz et al., teach the method step comprising administering the antibody conjugate to the prostate cancer patient and Liu et al.,

have providing the antibodies to the outer membrane of the PSMA which are better targeting the prostate cancer cells in vivo. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was

Applicant's arguments with respect to claims 34, 38, 40, 42, and 44-57 unpatentable over the Murphy et al., in view of Horoszewicz et al., have been considered but are moot in view of the new ground(s) of rejection above.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao,
Examiner
Art Unit 1642

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/Larry R. Helms/
Supervisory Patent Examiner, Art Unit 1643